18/ Declaration

Attorney Docket # 4948-2PCRCE

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Carlos PICORNELL DARDER et al.

Serial No.: 09/491,624

Filed: January 26, 2000

For: Oral Pharmaceutical Preparation Comprising an Antiulcer Activity Compound, and Process for its Production

Examiner: Amy E. Pulliam
Group Art: 1615

DECLARATION

DECLARATION in relation to Patent Application PCT WO 99/06032

The undersigned:

Carlos Picornell Darder, graduate in Pharmacy from the Universidad Complutense de Madrid, with address at Calle Machaquito 48, Madrid 28043,

Carmen Molina Millán, graduate in Chemical Sciences and Pharmacy from the Universidad Complutense de Madrid and doctor in Pharmacy from the Universidad Complutense de Madrid, with address at calle Virgen del Puig nº 9, 8º, 3ª, Madrid 27028, and

Lázaro Bravo Blanco, graduate in Pharmacy from the Universidad Complutense de Madrid, with address at calle Arte 16, 5ºE, Madrid 28033

HEREBY STATE AND SET ON RECORD THE FOLLOWING:

FIRST

One of the undersigned, Carlos Picornell, is the person shown as the inventor of Patent Application PCT WO99/06032.

The other two undersigned, Carmen Molina and Lázaro Bravo, are senior specialists in pharmaceutical technology, particularly as it relates to controlled-release dosage forms, and are currently employed by the company Liberación Controlada de Sustancias Activas, S.A. (LICONSA), which company is the present applicant for Patent Application PCT WO99/06032.

SECOND

We have performed experimental work to reproduce section 1) of example 6 of European Patent Application EP 0 642 797 and to obtain lansoprazole granules which, according to that document, are obtained by the procedure described. The aim of this work was to compare the resultant lansoprazole granules with those obtained from the procedure object of Patent Application PCT WO99/06032, particularly as described in example 1 of this patent application.

THIRD

Section 1) of example 6 of European Patent Application EP 0 642 797 literally discloses the following:

"1) Granules containing lansoprazole was prepared as follows.

Ingredients	mg
Lansoprazole	30
Magnesium Carbonate USP	22.4
Sugar Spheres NF	110.0
Sucrose NF	59.8
Starch NF	36.4
Low-Substituted Hydroxypropyl Cellulose NF (L-HPC-31)	40.0
Hydroxypropyl Cellulose NF (HPC-L)	1.4
Methacrylic Acid Copolymer LD (Eudragit L30D-55) (Röhm Pharma Co.)	44.6
Polyethylene Glycol NF (PEG-6000)	4.4
Titanium Dioxide USP	4.4
Polysorbate 80 NF (Rheodol TW-0120)	2.0
Talc USP	14.0
Colloidal Silicon Dioxide NF (Aerosil)	0.6
Purified water * USP	q.s.
Total	370.0

*: Removed during the manufacturing process
USP: The United States Pharmacopeia
NF: The National Formulary

Sugar spheres was coated with a mixture of lansoprazole, magnesium carbonate, sucrose, starch and L-HPC-31 by means of spraying aqueous HPC-L solution in a centrifugal fluid-bed granulator (CF-1000S, Freund Co.), and the resultant wet granules were dried in a vacuum oven at about 40° C for about 18 hours, and then sieved. The obtained granules were coated with aqueous enteric Eudragit suspension containing PEG-6000, talc, titanium dioxide and Rheodol TW-0120 in a fluid-bed coater (F10-Coater FLO-60, Freund Co.), and sieved, and then dried in a vacuum oven at about 42° C for about 18 hours. The obtained granules were mixed with talc and Aerosil."

This description omits a significant amount of data and parameters needed to use the procedure described, specifically omitting information on the following aspects related to the granulation step:

- Size of the sugar spheres comprising the core
- Concentration of the aqueous HPC-L solution to be sprayed
- Particle sizes of the solid excipients
- Conditions for introducing the solid mixture of active ingredient and excipients (pressure and rate of introduction) into the granulator
- Conditions for spraying the HPC-L binder solution (pressure and rate of spraying)
- Process temperature and volume of air

Moreover, in the complete text of European Patent Application EP 0 642 797 we have been unable to locate additional information or references that would allow the omitted data and parameters to be completed.

In view of this situation, we have attempted to supply the omitted data by applying our expertise in the field, endeavouring to maintain the essential aspects of the description without applying any inventive step that would alter the description contained in the document involved.

FOURTH

Using an MP-1-Roto Processor centrifugal fluid-bed granulator from the NIRO firm, we have performed pilot tests with the following amounts of starting materials:

Sugar spheres (cores of 500-600μm)	600 g
Lansoprazole	163.6 g
Magnesium carbonate	122 g
Sucrose	326 g
Starch	198.6 g
L-HPC-31	218.2 g
HPC-L (binder)	7.6 g

that maintain the weighted proportions described in example 6 of European Patent Application EP 0 642 797.

Since the envisaged amount of HPC-L binder is very small, it was used in the form of an aqueous solution of 5% by weight (151 g of solution), which represents the dilution allowing the largest amount of water while maintaining the binder capacity of the HPC-L. As a result, we attempted to make available sufficient water to complete the process of active coating of the inert sugar spheres.

The volume of air that allows the 600 g of sugar spheres to be kept in motion is 70-80 m^3/h.

The solid mixture is introduced at a pressure of 0.5 bar, allowing an introduction rate of 25 g/minute.

The spray rate of the 5% aqueous solution of HPC-L binder is at least 10-11 g/minute, which allows problem-free operation of the peristaltic pump at a spray pressure of 1 bar.

The process temperature is set at 30-35 °C.

Based on the stated introduction rate of the solid mixture (25 g/minute) and the total weight of this mixture (1028 g), the process takes at least 41 minutes. Nevertheless, some 15 minutes are needed to spray 151 g of 5% aqueous solution of HPC-L binder material at the required minimum spray rate (10 g/minute).

In order to make the solid mixture introduction time and the solution spraying time the same, the aqueous solution of binder material would have to be diluted still further . However, this is not possible since the binding capacity of the HPC-L decreases when the dilution is increased.

We consider that, as described in example 6 of European Patent Application EP 0 642 797, the weighted ratio of 1028:7.6 between the solid mixture and HPC-L binder material is too high for the process to be effective.

This aspect is critical, as confirmed by tests we have conducted that yield completely inappropriate results in which more than half the solid mixture has still not been loaded in the centrifugal granulator by the time the binder solution has been entirely sprayed. Moreover, the equipment was left with too much powder not adhered to the granules.

Therefore, as it is described in section 1) of example 6 of European Patent Application EP 0 642 797, the procedure in question does not yield lansoprazole granules suitable for subsequent enteric coating. Consequently, the use of the above procedure does not produce granules equal or similar to those obtained by the procedure object of Patent Application PCT WO 99/06032, particularly as described in example 1 therein.

FIFTH

Based on what we have stated in the fourth point, in order to ensure a sufficient amount of aqueous solution of binder material to complete the introduction of the solid mixture, we repeated the experiment with all the same parameters except for the amount of 5% HPC-L binder material, which was increased more than three-fold. In other words, we employed 485 g of 5% HPC-L solution, which represents an overage of 319% with respect to the HPC-L amount indicated in example 6 of European Patent Application EP 0 642 797.

Once the granulation step was completed and before proceeding to the enteric coating step, the following was observed:

(a) The process yield was only 85% because part of the solid mixture did not adhere to the granules. Consequently, powder remained on the equipment walls.

(b) The resultant granules were screened in cascade to between 700 and 125 microns, and it was observed that 18% of the particles had sizes below 600 microns and were inappropriate, while 81.3% had a particle size above 600 microns.

(c) Observation of the particles under an optical microscope revealed that the particles were not spherical and that roundness values were far from one. Only 1% of the particles had a roundness value between 1.05 and 1.1, while 26.47% had values between 1.10 and 1.15 and the rest had values above 1.15, sometimes being as high as 1.5.

(d) The particle appearance was highly irregular, being glassy on occasion, leading us to believe that these cases consisted in remains of solid mixture not adhered to the granules.

(e) The granules were excessively fragile, producing considerable amounts of dust when handling the bags that contain the granules (low mechanical strength).

We used the resultant granules to perform the coating step in an Aeromatic Fielder MP-4-RP-F2 Multi-processor from the NIRO company, in accordance with the data and parameters described in example 6 of European Patent Application EP 0 642 797.

Despite working with volumes of air around 250 m^3/h, the fragility of the resultant granules meant that the granules broke in significant proportions, causing the equipment to be heavily coated with dust.

Because the granules broke, lansoprazole came into contact with the enteric coating polymer (Eudragit). This interaction resulted in degradation of the active ingredient as seen by the formation of a dark brown colouring.

In order to minimise degradation of the active ingredient, a slow spray rate of around 10 g/minute was used to minimise excess moisture that would favour interaction between lansoprazole and the Eudragit polymer.

Nevertheless, the resultant coated granules had an intense dark brown colouring that indicated significant degradation of the active ingredient.

When the resultant coated granules were tested to determine the resistance to gastric fluid as described in the European Pharmacopoeia and USP-25, a value of 9.3% was obtained. This is an unacceptably low value, since the amount of active ingredient remaining in the dosage form after the gastro-resistance test would be expected to be no less than 90% of the label amount.

HPLC assay of the lansoprazole content of the resultant coated granules showed a value of 75 mg/g, an unacceptable deviation with respect to the theoretical amount (99 mg/g).

Therefore, even after correcting the defect of the procedure described in section 1) of example 6 of European Patent Application EP 0 642 797 in relation to the quantity of binder material, this procedure does not yield enteric-coated gastroresistant granules of lansoprazole that are appropriate and acceptable from the pharmaceutical standpoint. Consequently, the use of the above procedure does not yield granules equal or similar to those obtained with the procedure contemplated in Patent Application PCT WO 99/06032, particularly as described in example 1 therein.

SIXTH

We have performed the experimental tests mentioned in this declaration of good faith, applying our expertise and experience as experts in pharmaceutical technology in a way that we sincerely believe to be correct.

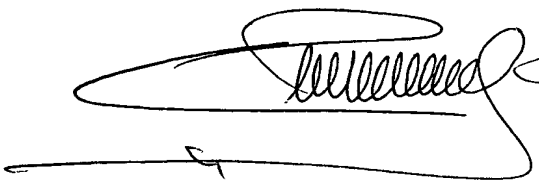
As a result, we expressly state that the conclusions we have reached correspond to reality and we are convinced that they are correct.

That all the statements made herein of their own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that wilful false statements may jeopardise the validity of Application Serial No. 09/491624 or any patent issuing thereon.

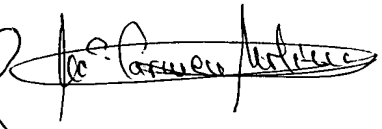
Madrid, 4th October 2002.

Signed

Carlos Picornell Darder



Carmen Molina Millán



Lázaro Bravo Blanco